Efficacy of Tranexamic Acid in preventing post operative blood loss and associated complications in bone sarcoma patients treated with limb salvage surgery: A randomized controlled trial.

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STUDY PROTOCOL

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Introduction:

Limb salvage surgery for malignant bone tumors results in extensive bone and soft tissue resection which leads to massive bleeding and requiring a large number of transfusions [1] [2]. Blood transfusions have their own complications like hemolytic reaction, graft versus host disease, the spread of infection and sometime can lead to mortality [3]. Blood loss and related complications may lead to high risk of reoperation, an increased hospital stay, and increases burden over the health resources especially among anemic cancer patients [4].

Tranexamic acid (TXA) is a synthetic analog of lysine that prevents fibrinolysis by blocking the lysine binding sites on plasminogen and it has been extensively used over the past decade in orthopedic surgeries to decrease perioperative blood loss and the transfusion rate [5][6]. Perioperative use of TXA has been shown to reduce intraoperative and postoperative blood loss and to decrease transfusion rates in both total knee arthroplasty and total hip arthroplasty [7][8]. Furthermore, it results in higher postoperative hemoglobin, decreased postoperative pain, swelling, length of hospital stays, and higher patient satisfaction [9][10].

Although there is a long-standing concern about TXA-induced hypercoagulability that may increase the risk for postoperative venous thromboembolism (VTE), there are multiple studies even in high-risk patients supporting its safe use [3][11]. In a review of more than 1,000 patients, 240 of which had multiple risk factors for embolic disease including known prothrombotic conditions, those who received TXA had no additional thrombotic events [12]. In addition, two studies have documented an overall reduction in healthcare costs due to fewer transfusions.[11][13].

Despite ample research documenting the safety and efficacy of perioperative TXA in patients undergoing arthroplasty, there is no known clinical trial focusing on TXA's use in musculoskeletal oncology patients undergoing endoprosthesis reconstruction. Nonetheless, TXA is used within the musculoskeletal oncology community, with its use varying from surgeon to surgeon. Surgeons who use TXA do so with the intent of limiting perioperative blood loss and transfusion rates in these high blood-loss procedures. However, without clinical trial to support its use in this cohort, these patients, who tend to have an increased number of comorbidities, could be inheriting an increased risk of perioperative complication without the benefits documented. Conversely, patients within this cohort that do not receive TXA could be missing out on the clinical benefits of TXA seen in patients undergoing arthroplasty. This randomized clinical trial will determine the efficacy of tranexamic acid in musculoskeletal oncology population who underwent wide local excision and reconstruction with endoprosthesis and will result in the formation of a guideline about its efficacy in reducing blood loss and adverse events that can be resulted by the use of tranexamic acid in the musculoskeletal oncology population.

Objectives:

To determine the efficacy of tranexamic acid in musculoskeletal tumor who underwent wide local excision and reconstruction with endoprosthesis and determine adverse events that can be resulted by the use of tranexamic acid.

Primary outcome measures:

Blood loss in a surgical patient can be monitored by:

- Drop-in hemoglobin in 72 hours
- The number of transfused PRBC unit
- 72-hour total blood loss as calculated by hemoglobin balance method

Hemoglobin balance method:

The Hemoglobin - balance method is based on the balance of Hemoglobin during the perioperative period of surgery. It is regarded as an important method with intuitive expressiveness and high accuracy and often addresses contemporary clinical issues [14]

$Hb_{loss\ total} = BV \times (Hb_i - Hb_e) \times 0.001 + Hb_t$	$Hb_{loss\ total}$ (g): The loss volume of Hb
$V_{loss\ total} = 1000 \times Hb_{loss\ total}/Hb_i$	Hb_i (g/L): The Hb value before surgery
Generally, 1 U banked blood is considered to contain 52 ± 5.4 g Hb[5]	Hb_e (g/L): The Hb value after surgery;
	Hb_t (g): The total volume of blood transfusion

Secondary outcome measures:

- Thromboembolic events: to be observed over six weeks from the date of surgery
- Hospital stay
- drain output till 72 hours

Methodology

Study Design: A Randomized control trial (RCT)

Setting: Department of surgical oncology, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore.

Sample size:

Sample size was calculated on the basis of previous study published by Haase, Douglas R.in 2020. Mean post-operative blood loss in TXA group and non TXA were 981±290 mL and 1542±394mL, respectively. [02] At 80% power, 95% confidence interval, assuming 10% drop out rate, a total of 36 patients included in this study divided into two groups (18 in each group, TXA versus non TXA) would be required in this study.

Sample selection:

Inclusion criteria:

Patients with primary or metastatic bone tumors who underwent a resection and an endo-prosthetic reconstruction of the proximal femur, distal femur, proximal tibia and proximal humerus. All patients will be tested for liver function using PT (INR), renal function by serum creatinine and Marrow function by CBC

Exclusion Criteria:

- Patient with a congenital or acquired coagulopathy
- Severe renal or liver insufficiency
- Previous thromboembolic condition
- A patient who received perioperative plasma product
- Pelvic tumor
- Patient who is taking anti-coagulant before surgery
- Patient allergic to tranexamic acid

Enrollment duration: Being a dedicated cancer center, a large number(30-40 per year) of Limb salvage surgeries are performed at Shaukat Khanum Memorial Cancer Hospital. The above-given sample size can therefore be achieved in 10 months.

Dose of tranexamic Acid: A single dose of tranexamic acid will be given intravenously at time of induction according to body weight i.e., 15 mg/kg

Anti-coagulation Protocol: All limb salvage patients started on anticoagulant Injection Enoxaprin subcutaneously after 24 hours of surgery according to body weight i.e. 1.5 mg/kg. Enoxaprin converted to oral tablet Aspirin 75 mg on discharge for 4 weeks.

Study Duration: 12 months after the start of enrollment.

In house admission: Limb salvage surgery patients remain admitted on the floor for an average of 5 days

Follow up Schedule: Physical follow up in clinic 2 weeks after surgery (as per institutional guidelines) and a second follow up at 4 weeks after surgery

Randomization: Intraoperative randomization, patients would be allocated to either of the groups by selecting names from sealed envelopes.

Type of randomization: Computerized block randomization. This will ensure a similar number of patients in both groups. Patients will have their names written on an envelope with contents of the envelope indicating whether tranexamic acid should be given or not. Only one member of research team will be aware of the contents of the envelope, who will not be present in Operation Theater at the time of surgery and will not take part in data collection. Patient in control group will be given 10 cc of normal saline as as placebo.

Blinding: It will be a triple-blind trial since the patients will be unaware of the group to which they have been randomized. The statistician carrying out data analysis and examiners/interviewers carrying out clinical examinations/interviewing patients will also be unaware of the status of tranexamic acid.

Minimizing Bias: It is not possible to eliminate bias altogether. However, the performance bias of the operating surgeon will be limited by not revealing the contents of the sealed envelope. The interviewer's bias will be limited by ensuring that the interviewer is not aware of tranexamic acid status at the time of the interview and by ensuring a standardized interaction between the patient and interviewer.

Intervention: Surgeon who will carry out Limb salvage surgeries, will be a consultant with > 5-year experience in Limb salvage. A single standardized technique will be used in all of the patients.

There is a difference of opinion about the use of tranexamic acid in surgeons at SKMH and both surgical options are practiced. The trial will therefore pose no additional risks to the patients.

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PROFORMA

Full Name: _____

MR Number: _____

Date of Surgery: _____

Age_____Years

Sex:

- **Male**
- **Female**

Co-Morbid:

- **HTN**
- **DM**
- **CVA**
- **IHD**
- **Others**

Type of Malignant Bone Tumor:

- **Ewing Sarcoma**
- **Osteosarcoma**
- **PNET**
- **Other**

Site of Primary Tumor:

- **Humerus _____**
- **Femur_____**
- **Tibia _____**
- **Other**

Group:

- **Tranexamic Acid Given**
- **Tranexamic Acid Not Given**

Length of Bone Resected____Cm

Wound Healing: (Satisfactory / Unsatisfactory)

Preoperative Hemoglobin_____gms

Preoperative INR_____

Intraoperative Blood Loss:_____mls

Postoperative Hemoglobin after 24 Hours____gms

Postoperative Hemoglobin after 72 Hours_____

Number of PRBC Transfused Within 72 Hours of Surgery_____

Blood Loss Calculated By Direct Hemoglobin Method_____

Drain Output in 72 Hours:_____mls

Any Thromboembolic Event: _____

Status of Ambulation:

STATISTICAL ANALYSIS PLAN:

Statistician independently pooled data from each case then conducted statistical analysis using SPSS Descriptive data are presented as mean ± standard deviation (*SD*). Odds ratio (*OR*) with 95% confidence intervals (*CI*) or mean differences (*MD*) with 95% *CI* were calculated for dichotomous and continuous outcomes, respectively. Numerical and measured data were compared using a *t*-test and χ^2-test, respectively. An appropriate power and sample size calculator was used to calculate statistical power. The following parameters were used in the calculations: α, probability of a type I error for a two-sided test; P0, probability of exposure in controls; *N*, number of patients; m: ratio of control to experimental subjects; and Ψ, odds ratio of exposure in experimental subjects relative to controls. $P < 0.05$ was considered significant.